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10/573,969	03/30/2006	Takeyuki Sugiura	Q94181	9936

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	PAPER NUMBER
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/573,969	SUGIURA, TAKEYUKI	
	Examiner	Art Unit	
	IQBAL H. CHOWDHURY	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *1-15,19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/06, 07/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are currently pending.

This application is a 371 of PCT/JP04/14812.

Election/Restriction

Applicant's election with traverse of Group V claim(s) 16-18, drawn to a method of diagnosing colon cancer by detecting nucleic acid molecule of nucleotide sequence of from 94th to 2934th of SEQ ID NO: 1 encoding a polypeptide of SEQ ID NO: 2 or detecting nucleic acid molecule of SEQ ID NO: 1 encoding polypeptide of SEQ ID NO: 2 in the communication filed on 06/01/2007 is acknowledged.

The traversal is on the ground(s) that lack of unity established by the Examiner is not proper. Applicants argue that the reference (WO 2002/083873) cited by the Examiner, do not teach the function of the nucleic acid molecule encoding protein of cell growth accelerating activity.

This is not found persuasive because the reference indeed teach that said protein is "crucial to proliferating cells" (page 3, line 12), i.e. crucial to cell growth". Besides, since, the reference teaches the nucleic acid molecule, which is 100% identical to SEQ ID NO: 1 of the instant application (see sequence alignment) as well as encoding said protein of the instant application, the cell growth accelerating activity is the inherent property of the protein.

As discussed in the previous office action regarding lack of unity of the various inventions of the instant application, the Examiner states that "The inventions listed as Groups I - VI do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following

reasons: the DNA of Groups I, polypeptide of Group II, antibody of Groups III, and therapeutic agent of Group VI are each unrelated and chemically distinct entities. The only shared technical feature of these groups is that they all relate to polynucleotide encoding said polypeptide. However, this shared technical feature is not a "special technical feature" as defined by PCT Rule 13.2 as it does not define a contribution over the art. According to the search report, a DNA encoding polypeptide having said activities are known in the art (WO/2002/083873, published on 10/24/2002, see IDS), which is 100% identical to SEQ ID NO: 1 of the instant application. Thus, a DNA encoding a polypeptide having said functions does not make contribution over the prior art. Therefore, Groups of inventions I-VI lack special technical feature and lack unity of inventions.

As mentioned above, SEQ ID NO: 1 is known in the art and does not make contribution over the prior art. Therefore, all the Groups, lack special technical feature at the same time lack unity of invention. Besides, searching all the groups would create a serious search burden to the Examiner because searching all the groups require nucleic acid sequence, and protein sequence search, which includes mutants and variants as well as Patent and non-Patent literature search, which would create a serious burden to the Office.

As restriction is clearly permissible even among related inventions as defined in MPEP 808 and 35 U.S.C. 121.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 1-15 and 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

Claims 16-18 are present for examination.

Priority

Acknowledgement is made of applicants claim for foreign priority under 35 U.S.C. 119(a)-(d) to a foreign patent application 2003-341245 (JAPAN) filed on 09/30/2003 without English translation.

Information Disclosure Statement

The information disclosure statements (IDSs) submitted on 03/230/2006 and 07/25/2006 are acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are considered by the examiner. The signed copies of IDSs are enclosed herewith.

Drawings

Drawings submitted on 03/30/2006 are accepted by the Examiner.

Claim Objections

Claims 16-18 are objected to as depending from non-elected claims. Appropriate correction is requested.

Claims 17-18 are objected to in the recitation "The judging method" which should be "The method". Appropriate correction is requested.

Claims 16-18 (which depend on claims 1-4) are objected to in the recitation "DNA represented by", which should be "DNA comprising". Appropriate correction is required.

Claims 16-18 (which depend on claims 1-4) are objected to in the recitation "nucleotide sequence described in SEQ ID NO: 1", which should be "nucleotide sequence of SEQ ID NO: 1". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 16 and 17 are indefinite as reciting methods with **no** steps. Accordingly, claim 18 is also rejected as it depends on claim 17.

Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim16 recites, "characterize in that" which is unclear. Examiner has suggested deletion of the above phrase and replacing it with the term "wherein". Accordingly, claims 17-18 are also rejected as they depend on claim 16.

Claims 16-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite and vague for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the present instance, claim 16 part (4) recites "judging whether or not ----" is vague, which is unclear as to what steps or procedures that are encompassed. Accordingly, claims 17-18 are also rejected as they depend on claim 16.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-18 (which depend on claim 4) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 16-18 (based on the scope of claim 4) are directed to a method of diagnosing a colon cancer by detecting any nucleotide sequence of SEQ ID NO: 1, wherein any one or more bases are deleted, substituted or added to SEQ ID NO: 1. Claims thus, directed to a process of using in any nucleotide sequence with or without relation with the encoded protein of SEQ ID NO: 1. As discussed in the written description guidelines the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The specification teaches the structure of only a single representative species of such nucleic acid molecule of SEQ ID NO: 1 encoding a protein of SEQ ID NO: 2. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding the

polypeptide having cell growth accelerating activity. Given this lack of description of representative species encompassed by the genus of DNAs used in the methods of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 16-18 (which depend on claim 4) are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing colon cancer by detecting nucleic acid molecule of a nucleotide sequence from 94^{th} to 2934^{th} of SEQ ID NO: 1 encoding a polypeptide of SEQ ID NO: 2 having 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities and cell growth accelerating function or detecting nucleic acid molecule of SEQ ID NO: 1, wherein said nucleic acid molecule encoding a polypeptide of SEQ ID NO: 2 having 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities and cell growth accelerating function, does not reasonably provide enablement for a method of diagnosing colon cancer by detecting any nucleotide sequence of any protein, wherein one or more bases are deleted, substituted or added to the nucleotide sequence of SEQ ID NO: 1 and encodes a protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands (858 F.2d 731,737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows:

(1) quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence and absence of working examples, (4) the nature of the invention, (5) the state of prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The factors, which have, lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed below:

The breadth of the claims:

Claims 16-18 (which depend on claims 1-4) are so broad as to encompass a method of diagnosing colon cancer by detecting any nucleic acid molecule of any protein having one or more bases are deleted, substituted or added to the nucleotide sequence of SEQ ID NO: 1. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of genes encoding proteins including many mutants, variants and recombinants due to one or more bases are deleted, substituted or added to the nucleotide sequence of SEQ ID NO: 1 broadly encompassed by the method of the claims. In the instant case the disclosure is limited to the nucleotide sequence of SEQ ID NO: 1 and encoded amino acid sequence of only a single protein of SEQ ID NO: 2 having 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities and cell growth accelerating function. The scope of claim 16 is also not commensurate with the enablement provided by the disclosure with regard to correlation with the amount of expressed DNA and colon cancer diagnosis.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art:

The amino acid sequence of a polypeptide determines its structural and functional properties. While the specification discloses a single nucleotide sequence of SEQ ID NO: 1 and encoded amino acid sequence of only a single protein of SEQ ID NO: 2 having 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities for detecting said nucleotide sequence by the method of the claim, neither the specification nor the art provide a correlation between structure and function and disease state such that one of skill in the art can envision the structure of any nucleotide sequence encoding protein having one or more bases are deleted, substituted or added to the nucleotide sequence of SEQ ID NO: 1 used in the claimed method for diagnosis of colon cancer. The art clearly teaches that modification of a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are tolerant of modification and which ones are conserved is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (1991) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing de novo stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (1999) and Seffernick et al. (2001), where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required practicing the claimed invention based on the teachings of the specification:

While methods of detecting variants of a polynucleotide were well known in the art at the time of invention, it is not routine in the art to screen by trial and error process for (1) any nucleotide sequence of any protein encoded by SEQ ID NO: 1 due to deletion, substitution, or addition of one or more bases to the nucleotide sequence of SEQ ID NO: 1, and (2) an essentially infinite number of mutants or variants of any gene encoding any protein sequence to be detected by the methods of the claim for diagnosis of colon cancer. The amino acids modifications by changing the any bases by deletion, substitution or addition of one or more bases to SEQ ID NO: 1 can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple point mutations or substitutions. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification.

The amount of direction or guidance presented and the existence of working examples:

The specification discloses a method of diagnosing colon cancer by detecting nucleic acid molecule of nucleotide sequence from 94^{th} to 2934^{th} of SEQ ID NO: 1 encoding a polypeptide of SEQ ID NO: 2 or detecting nucleic acid molecule of SEQ ID NO: 1 by using primers of SEQ ID NO: 5 and 6, wherein said nucleic acid molecule encoding a polypeptide of SEQ ID NO: 2 having 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities and cell growth accelerating function for diagnosis of colon cancer. However, the specification fails to provide any clue as to the

structural elements required in any nucleotide sequence of any protein encoded by SEQ ID NO: 1 due to deletion, substitution, or addition of one or more bases to the nucleotide sequence of SEQ ID NO: 1 known in the art that are essential for any protein to display said enzyme activities as well as cell growth accelerating function or correlation with colon cancer. No correlation between structure and function has been presented.

The specification does not support the broad scope of the claims which encompass any nucleotide sequence of any protein encoded by SEQ ID NO: 1 due to deletion, substitution, or addition of one or more bases to the nucleotide sequence of SEQ ID NO: 1 for diagnosis of colon cancer because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting enzymatic activity and; (B) the general tolerance of polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide sequence of any protein encoded by SEQ ID NO: 1 due to deletion, substitution, or addition of one or more bases to the nucleotide sequence of SEQ ID NO: 1 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any nucleotide sequence of any protein encoded by SEQ ID NO: 1 due to deletion, substitution, or addition of one or more bases to the nucleotide sequence of SEQ ID NO: 1 for diagnosis of colon cancer. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without

sufficient guidance, determination of any nucleotide sequence of SEQ ID NO: 1 due to deletion, substitution and addition of one or more bases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 16 is rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al. (WO2002/83873, publication October 24, 2002, see IDS).

Instant claim is directed to a method of diagnosing colon cancer by detecting any nucleotide sequence of SEQ ID NO: 1 encoding any protein, wherein one or more bases are deleted, substituted or added to the nucleotide sequence of SEQ ID NO: 1 having 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities and cell growth accelerating function.

WO teaches a gene encoding a protein holoenzyme complex tetrahydrofolate synthase having trifunctional properties, i.e. 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities, which is 100% identical to SEQ ID NO: 1 of the instant application (p3, line 6-12, and see

sequence alignment). WO also teaches that said gene is expressed in cancer tissue including colon carcinoma. WO further teaches a method of diagnosis of a disease by detecting the expressed nucleic acid molecule (p103 and 104, line 2-7). Therefore, WO anticipates claim 16 of the instant application.

Claims 16-18 are rejected under 35 U.S.C. 102(a) as being anticipated by Sugiura et al. (A novel mitochondrial C1-tetrahydrofolate synthetase is upregulated in human colon adenocarcinoma, Biochem Biophys Res Commun. 2004 Feb 27;315(1):204-11, available online 24 January 2004).

Instant claims are directed to a method of diagnosing colon cancer by detecting any nucleotide sequence of SEQ ID NO: 1 encoding any protein, wherein one or more bases are deleted, substituted or added to the nucleotide sequence of SEQ ID NO: 1 having 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities and cell growth accelerating function.

Sugiura et al. teach a gene encoding protein of C1-tetrahydrofolate synthetase having trifunctional properties, i.e. 10-formyl-tetrahydrofolate synthetase, 5,10-formyl-tetrahydrofolate cyclohydrolase and 5,10-methylene-tetrahydrofolate dehydrogenase activities, which is an mitochondrial enzyme, which is 100% identical to the encoding protein of SEQ ID NO: 1 of the instant application (see sequence alignment). Sugiura et al. also teach that said gene is upregulated to colon adenocarcinoma tissue, which is about 3 fold than normal colon tissue. Sugiura et al. further teach that identification of said gene expression could be a prognostic marker for colon cancer. Furthermore, Sugiura et al. teach a method of detection of said gene

expression, such as RT PCR for reverse transcription of mRNA of said gene followed by polymerase chain reaction (PCR) by using forward and reverse primers. Therefore, Sugiura et al. anticipate claims 16-18 of the instant application.

Conclusion

Status of the claims:

Claims 1-20 are pending.

Claims 1-15 and 19-20 are withdrawn.

Claims 16-18 are rejected.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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